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Editorial

Preventing Occupational Cancer

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The classic episode in the history of disease prevention occurred in London in 1854 (*1*). There was an epidemic of cholera in the neighborhood around Broad Street. John Snow, the hero of the story, studied the habits of the victims and found that almost all obtained their water from the well on Broad Street. Swift action was taken; the pump was closed down and the epidemic rapidly subsided. This action was taken before there was a clear understanding that the disease was caused by exposure to the bacterium *Vibrio cholerae*. One can imagine the reaction that might occur today if it were proposed to close down the pump on the basis of evidence of the kind obtained by John Snow. Many scientists would point out that it had not been conclusively demonstrated that the water was the cause of the disease. They would be troubled because of the lack of satisfactory theoretical knowledge to explain how the water could have caused the disease. Furthermore, other habits of those who had become ill had not been adequately investigated, so it would not be possible to rule out other causes of the disease. These scientists would have been correct. Others would have pointed out that some members of the community who drank from the Broad Street well had not succumbed to cholera. Thus, even if there were something wrong with the water, there must be other factors involved, and if these could be controlled, they would not have to be concerned about the water. These conclusions are also correct. Some who consumed water from the Broad Street well would have objected to closing it because it was inconvenient to get their water elsewhere or because the taste of water from other wells was not as agreeable. Finally, if the pump had been owned by an individual who sold the water, he would certainly have protested against closing down his business on the basis of inconclusive evidence of hazard.

Although this story is about an infectious disease, it illustrates a number of points that are also relevant to the prevention of cancer or other kinds of injury from toxic chemicals. First, if human disease and deaths are to be prevented, it is often necessary to control exposure to chemicals for which there is some evidence of hazard before that evidence has reached the point that scientists would universally regard as conclusive. The alternative, to continue exposure until there is conclusive evidence of human hazard, is a form of human experimentation that our society finds increasingly unacceptable.

Second, development of a disease in any individual is the result of complex interactions of a variety of factors including his or her genetic susceptibility; environmental influences on the person's state of susceptibility that may include such things as exposure to other substances in the environment, the person's state of nutrition, age, and general health; and finally the level and extent of exposure to specific disease causing agents. These principles hold true for cholera; not all who drank from the Broad Street well developed cholera. These principles also apply to cancer induction; cancer develops in susceptible individuals exposed to carcinogenic agents.

Third, the incidence of disease in a population can be reduced either by reducing exposure to specific causative agents or through general or specific measures that reduce the level of susceptibility of the population to the causative agents. The state of our knowledge about the specific disease determines which measures can be applied most successfully at any particular time in history. During John Snow's time, removing the supply of contaminated water was the most feasible approach. Today, cholera can also be controlled through immunization and mortality can be reduced through specific therapy. During John Snow's time, however, the latter options were not available. In the control of tuberculosis, good nutrition and good living conditions are as important as removing the source of exposure to the bacteria through hos-

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pitalization of diseased individuals (*2*). These general health measures increase resistance of the population to the disease agent. More specific immunization techniques against tuberculosis have been developed; but their effectiveness has been a matter of considerable debate for many years (*3*).

For cancer, the major method of prevention available today is to prevent exposure to chemicals and radiations capable of inducing the disease (*4*). There is no doubt that genetics plays a part in susceptibility of individuals to cancer (*5*), but we cannot control the genetics of the population. Nutrition can undoubtedly affect the susceptibility of an individual to cancer. The obese have a higher incidence of cancer than those of normal weight (*6*). In addition, diets from various countries appear to be associated with specific kinds of cancer (*7*). For example, there is a high incidence of cancer of the stomach in those living on the Japanese diet and a high incidence of cancer of the colon and pancreas in people consuming a typical American diet (*8*). Whether these differences result from the presence of specific carcinogenic agents in food consumed or result from the effect of these diets on susceptibility to carcinogenic agents from other sources of exposure is currently unknown. Some have recommended what they call a "prudent" diet, thought likely to result in a lower susceptibility to cancer. It may take a number of years to learn how effective this will be.

We do know, however, that prevention of exposure to carcinogenic chemicals and irradiations can be remarkably effective in preventing the kinds of cancer they induce. Cancer of the lung, the most common cancer among males in the United States, is uncommon in those who do not smoke cigarettes (*9*). Stopping smoking reduces the risk for former smokers (*10*). Cancer of the skin results from excessive exposure to sunlight (*11*). Genetic factors in susceptibility and resistance are well demonstrated by this form of cancer. Dark-skinned populations are resistant, whereas light-skinned are relatively susceptible. The most susceptible individuals have a rare genetic trait called xeroderma pigmentosum. These individuals have a genetic defect that prevents them from repairing damage from ultraviolet irradiation (*12*). Their susceptibility is so severe that, in the past, those with the defect have always died from skin cancer in their adolescent or early adult years. There is now evidence, however, that even in the case of such extreme genetic susceptibility, removal of exposure to the causative agent can prevent the disease. Children with xeroderma pigmentosum who have been kept out of sunlight have not developed skin cancer (*13*). Although the genetic defect that makes these people highly susceptible to skin cancer cannot be corrected, they can be prevented from developing skin cancer by preventing exposure to the carcinogenic ultraviolet rays of the sun.

Thus, the development of cancer is dependent both on the level of exposure to carcinogenic agents and on multiple environmental and genetic factors affecting the individual's state of susceptibility. This concept is often lost sight of even among scientists. A recent publication (*14*), for example, divides cancers of "preventive potential" into those "attributable to" diet, tobacco, radiation, occupation, alcohol, and exogenous hormones. The total adds up to 100%. Consideration of the complex multiple interactions of environmental and host factors involved in cancer induction suggests that the sum of these individual contributions to cancer induction in the American population should be significantly greater than 100%. Even among occupational groups that have been heavily exposed to potent chemical carcinogens, some of the workers have remained free of cancer (*15*). Other factors must distinguish between those who develop cancer and those who do not. The way in which these individuals metabolize the carcinogenic chemicals, either to metabolites that directly induce cancer in the exposed cells or to harmless ones, is undoubtedly one factor determining whether or not an individual will get cancer. Metabolism appears to be partly under genetic control (*16*) but is also influenced by the diet (*17*) and by exposure to drugs or other environmental chemicals (*18*). Thus, it is more reasonable to expect that the workers who develop cancer after being exposed to an occupational carcinogen do so as the result of their exposure to the occupational carcinogen, their genetics, their diet, and their exposure to other environmental chemicals than to simply classify these carcinogens as occupationally induced without also tabulating the responsibility of these other factors in their causation.

There is evidence for a synergistic action of cigarette smoking and exposure to asbestos in the induction of lung cancer (*19*). Thus, some cigarette smokers would not have developed cancer if they had not had an occupational exposure to asbestos and some asbestos workers would not have developed cancer if they had not smoked cigarettes. How can these cancers be neatly attributed to either tobacco or occupation? Both causative factors are important.

Most patients with xeroderma pigmentosum would not have developed skin cancer if they had not been so unlucky as to inherit the genetic defect. Likewise, they do not develop skin cancer unless they are exposed to ultraviolet light. Should we

classify skin cancer in xeroderma pigmentosum patients as a genetic cancer or as a cancer resulting from exposure to ultraviolet light? Actually it is both, and it is an oversimplification to try to classify it as simply one or the other.

Viewed in this light, cancer being the result of multiple factors of exposure and susceptibility, it is difficult to place a true estimate on the contribution of exposure to occupational carcinogens to the total incidence of cancer in the United States. Few epidemiologic studies of occupational cancer have been of adequate sensitivity to detect anything smaller than a 50% increase in the incidence of cancer over that found in the general population (*20*). Weakly carcinogenic agents, that is, those capable of inducing cancer only in the most highly susceptible individuals at the level to which the worker population is exposed, would not be detected by most epidemiologic studies. Nevertheless these chemicals could still result in an unacceptable risk of cancer in exposed workers. There is some evidence that carcinogens brought home from the workplace on clothing may increase the incidence of cancer in members of the worker's families (*21*). In addition, it is reasonable to believe that the high incidence of cancer in counties surrounding some chemical and other industrial plants may result from exposure of the local population to inadequately contained industrial carcinogens (*22*). Individuals in these communities are also of diverse genetic stock and exposed to other chemicals and diets that may affect their susceptibility to cancer. Depending upon whether these people were included in a large study of diet as a factor influencing cancer incidence or a study comparing cancer in industrialized communities with rural communities, some of these cancers might be considered to be either of dietary or of industrial origin. Unfortunately, we are still in the situation with regard to cancer induction comparable to that of the blind men and the elephant. Where multiple factors of causation are involved, those being studied will be those that are observed. This does not indicate that other contributory causes are not involved in the same cancers. Prevention of cancer depends upon identifying whatever causative factors we can and controlling these wherever we can. Occupational carcinogens are among the causes that can be effectively controlled. With the increasing dependence of our society on synthetic chemicals, increasing vigilance will be required to maintain the health of workers.

If we are to identify chemical carcinogens before they have caused cancer in humans or if we are to identify chemical carcinogens that have not resulted in a sufficiently elevated risk of cancer induction to be shown by epidemiologic studies, we must depend on animal experiments.

It has been pointed out (*23*) that in an experiment with 100 animals, "each animal is surrogate for two million people" in this country. Whenever a regulatory decision is made or a regulatory policy contemplated, based on using experimental animals as human surrogates, the question of how precisely they reflect the true toxicologic risk to humans from exposure to the same chemicals always arises. The science of toxicology will have made immense strides when it becomes able to use the results of animal experiments to precisely predict the toxic risk of chemical to any individual or group of humans. Unfortunately we are not there yet. The problem is terribly complicated. Absorption, rate of metabolism, and excretion of environmental chemicals may differ somewhat among species (*24*). Species differ significantly in the types or relative ratios of metabolites formed from any chemical (*25*) and in the sensitivity of various organ systems to the toxic effects of these chemicals (*26*). Individuals within each of these species may show wide differences among these parameters (*27*) depending upon their genetics and on modifying environmental circumstances. Susceptibility in the same individual may fluctuate during the phases of various biological cycles (*28*). Although we know these variables exist, we do not have enough knowledge to weigh each of them in any particular case and come up with a reliable multiplier for converting results of animal experiments to risk for any individual human under his or her conditions of life. Science left to its own devices would respond to this situation by deferring judgment until adequate knowledge became available. In a functioning and ongoing economy, decisions must be made to either permit or prohibit human exposure before this level of certainty has been reached. Deferring judgment simply means that the status quo is maintained. Old chemicals remain in use; new chemicals will not be permitted to be used.

Much of the debate among scientists that occurs in relation to decisions by regulatory agencies is essentially a debate on how to weigh limited scientific information to decide whether a chemical does or does not pose a health hazard for humans. In the absence of scientific certainty, the same data will be interpreted differently by different scientists. Their interpretations are invariably colored by their own philosophies regarding the level of assurance of safety that should be provided before permitting human exposure to a chemical or the amount of evidence of hazard that should be demonstrated before steps are taken to prevent human exposure. Protestations that this is not the way science works cannot obscure the fact that science is "a very

human business'' (*29*) and that scientists will behave like human beings in their interpretation of evidence that is less than irrefutable. The real policy question, then, is deciding how less than irrefutable scientific knowledge shall be used to make a regulatory decision that may have an impact both on human health and on the economy. This involves a scientific determination of the most likely interpretation of available scientific information and a policy decision on whether to lean toward the side of protecting human health or the side of protecting economic enterprise when faced with scientific uncertainty.

There is much debate about the interpretation of animal experiments designed to detect chemicals that may be carcinogenic for humans. Although epidemiologic studies of exposed humans can make useful contributions to our understanding of human risk, they have several drawbacks. First, information on carcinogenicity of a chemical in humans is only obtained after many years of exposure and after harm has already been done to those who have been exposed. Second, although a positive result needs to be given very serious consideration, it is often difficult to be sure that the correlation noted between exposure to a chemical and an increased cancer rate is the result of the chemical; since these same individuals have probably been exposed to many other chemicals over a period of many years. Thus, additional epidemiologic investigations or animal experiments are usually required to confirm the original observation. Third, epidemiologic studies are usually of fairly limited sensitivity, especially when the exposed population is relatively small. That is, they can only detect substantial increases in cancer rates in the exposed population. Therefore, a negative result can be used to set an upper limit on the risk of cancer to humans exposed for the same time and to the same amounts of chemical as the population under study, but cannot eliminate the possibility that a lower level of risk may exist. For these reasons, we are usually forced to rely heavily on experimental studies as a basis for judging the potential carcinogenicity of a chemical for human beings. This practice is supported by the observation that most known human carcinogens are also carcinogenic in experimental animals (*30*), that for the most part the same kinds of metabolic enzymes that activate and detoxify chemical carcinogens are present in both human tissues and in experimental animals (*31*), and that the general process of development of similar kinds of cancer is comparable in humans and experimental animals (*32, 33*). The question is sometimes asked, ''Are there chemicals that have been shown to be carcinogenic in experimental animals that are not carcinogenic in humans?'' Although it is not unreasonable to anticipate that there might be some chemicals that are carcinogenic for some other species but not for man, we cannot answer this question definitively. Most chemicals shown to be carcinogenic in experimental animals have either been ones for which there has been little human exposure, or have been studied in too few people or for too short a period after exposure to rule out the possibility of their being able to cause cancer in man (*34*).

Animal experiments are usually conducted at considerably higher levels of exposure than those customarily occurring in humans, though in some poorly controlled occupational settings it is possible for workers to be exposed to high levels of carcinogenic chemicals (*35, 36*). Since this practice of testing at high dose levels is often challenged, some comments about it are in order. The fundamental reason for doing so is to enhance the sensitivity of the experimental bioassay to detect a chemical carcinogen. A study in 100 animals, a common size of experimental group at the present time, can obviously not detect anything lower than the induction of cancer in one percent of the animals. In actual practice, statistical considerations permit only the detection of a risk severalfold larger than this for rare tumors and considerably larger if the types of tumors induced are those found with significant frequency in untreated control animals. This level of risk is much higher than that which is socially acceptable in an exposed human population. In order to detect lower levels of risk, it is either necessary to test in much larger groups of animals or to test at much higher dosage levels than those to which humans are exposed and use mathematical procedures to estimate the level of risk from lower levels of exposure. The former approach can be utilized by any manufacturer who wishes to determine experimentally the levels of risk from low levels of exposure to his product, but in practice such an experiment would often have to be so large as to be unfeasible economically. The latter approach is economically feasible but is based on certain scientific assumptions that are debated. One of these assumptions is that there is no threshold below which exposure to a carcinogenic chemical entails no risk. That is to say, although decreasing the exposure will decrease the risk of cancer induction, there is no level below which the risk becomes absolutely zero until zero exposure is reached. Debate over this question is partly a matter of semantics or definition of terms. Some scientists approach this issue as a mathematical problem by which the likelihood of induction of cancer becomes very, very small as exposure becomes very, very small, but the possibility still remains. Others will conclude that when

the risk gets small enough it is the practical equivalent of zero. Thus, the first group might argue that a risk of one in one billion of inducing cancer in a finite (though perhaps tolerable) risk and not a threshold, while the other group may argue that for practical purposes this is so low as to be the practical equivalent of a threshold. More scientific arguments for threshold may point out the possibility that chemicals are metabolized differently at high exposure levels than at low levels, that protective mechanisms may be more effective at low exposure levels than at high ones, and that repair mechanisms may be more effective at low exposure levels than at high levels (*37*). In principle, these arguments can be used as arguments in favor of a threshold only if it can be shown that the carcinogenic metabolite present at high exposure levels is totally absent at low exposure levels (rather than simply present as a lower proportion of total metabolites), or that defense and repair mechanisms are totally effective (rather than proportionately more effective) at low exposure levels in contrast to high levels. In the absence of this information as a general principle or for any specific chemical under question, these arguments suggest that the risk from low levels of exposure may be less than otherwise might be projected from high exposure experiments, but they fail to provide convincing arguments for general concept of threshold.

The concept of threshold is also confused because some scientists use the term to apply to individuals while others use it to apply to populations. As discussed earlier, the sensitivity of any individual to a chemical carcinogen will vary depending upon his genetics, state of health, age, and exposure to a wide variety of environmental factors. Thus more resistant individuals may be able to tolerate an exposure level that would result in cancer for the more susceptible. If the term "threshold" is applied to these people, the same level of exposure may be below the threshold for carcinogenicity of the resistant individuals but above that for the sensitive ones. When these considerations are applied on a population basis, it can be seen that this level might increase the total incidence of cancer in a large exposed population even though the level might be one that could be tolerated by many individuals within it. Since approximately a quarter of the American population will develop some form of cancer during their lifetimes, it is apparent that many are already over their threshold and additional exposures are likely to push more over the limit. At the present time, we are still in a position of being unable to unequivocally decide whether or not thresholds exist, as defined at the molecular or population level, or to determine which individuals in the population may or may not be able to tolerate additional exposure from carcinogenic chemicals.

There are also debates about whether a variety of mechanisms may exist by which chemicals increase the incidence of cancer in a group of experimental animals, and whether these can be sorted out into mechanisms having differing levels of risk for humans under the conditions and levels of human exposure. This is a valid scientific question, but one difficult to answer for any individual regulated chemical without a very extensive research effort. Even at the general level of classes of chemicals, the principles to be used to sort out such groupings and to estimate the risks associated with them are not well understood. If such an attempt were made, one class would certainly consist of those chemicals that react with DNA and are capable of causing mutation (*38*), whether or not that is actually the mechanism by which cancer is induced. Probably a higher proportion of scientists believe that this class has no threshold than would agree on other classes. Another class would be promoting agents (*39*). In the experimental skin carcinogenesis model for which this terminology was developed, it is recognized that these agents have little or no carcinogenic effect themselves, that they markedly enhance the carcinogenicity of certain carcinogenic chemicals, and that their effect requires repeated exposure and is reversible in the absence of such repeated exposure. Since the mechanism by which this effect occurs in the skin has still not been adequately worked out, it is difficult to know how widespread this precise phenomenon is for various chemicals and organ sites. Thus, although this is a class of chemical affecting the incidence of cancer that many would regard as likely to have a threshold, there are usually practical problems involved in deciding whether or not a chemical should be placed in this class from the amount of data generally available to the regulator. There are also problems involved in determining the level at which a threshold may exist, and little information is available on how a multiplicity of promotors and other chemicals in the human environment may interact in an additive, synergistic, or inhibitory way to affect the level at which a threshold for promoting agents may lie (*40*).

Another class of chemical consists of those having hormonal effects. Most scientists in the field of toxicology and chemical carcinogenesis believe that these act by a mechanism different from those chemicals that are both carcinogenic and mutagenic. The evidence for this is not conclusive, however. It will probably remain subject to debate until there is a definitive understanding of the mechanism by which carcinogenic hormones cause cancer. Even if this mechanism is different from

those of mutagenic chemicals, two questions still remain. First, are there thresholds for such effects? Second, if a synthetic chemical is carcinogenic and has a hormonal action, is this the only mechanism by which it can cause cancer? On the threshold question, the assumption is often made that since hormones are natural chemicals of the human body, there are levels that are noncarcinogenic and a small incremental exposure over natural levels will have no significant effect. This overlooks the fact that a substantial proportion of human cancers occur in organs under the control of hormones even among individuals who have never received synthetic hormonal chemicals. Thus, "normal" levels of exposure do appear to be related to the development of cancer in some people. A small increase in those levels may have a small impact on the total cancer incidence, but is not necessarily negligible. The problem with the second question is illustrated by the drug, diethylstilbestrol. This drug is carcinogenic in experimental animals (*41*) and has been shown to cause cancer of the vagina in the offspring of some women who were treated with it during pregnancy (*42*). It almost certainly can induce cancer through the same mechanism as natural estrogens, but it also can be metabolized to products that may be capable of binding to DNA (*43*) and therefore may act through another mechanism of carcinogenesis as well.

It is known that the caloric content of the diet can influence tumor incidence, both in experimental circumstances (*44, 45*) and, as indicated by obesity, in humans (*6*). This effect could influence the interpretation of an experiment in which caloric intake were not controlled among different groups of animals. Increased caloric intake is associated with an increased incidence of cancer, whereas a decreased caloric intake reduces the cancer incidence. In the common types of bioassay protocols in which animals are fed *ad libitum*, it is ordinarily those receiving maximum exposure of the chemical that eat the least. Thus, this effect would tend to underestimate the risk of cancer induction in heavily exposed animals.

Another debated issue is the significance of benign tumors as an index of carcinogenicity of a chemical. This subject has been discussed by many groups of scientists who have issued recommendations on the interpretation of carcinogenicity studies. Depending upon which report is read, one will receive the advice either to base the assessment of carcinogenicity only on the presence of malignant tumors (*46*), on both malignant and benign tumors (*47*), or on malignant and benign tumors when both are present in the same organ, but not on benign tumors when malignant tumors are not also present (*48*). Thus, this is certainly an issue on which unanimity of scientific opinion does not prevail. In analyzing this issue it is helpful to consider the circumstances under which the distinction between benign and malignant tumors developed and how these apply to the problem of determining whether or not a chemical is capable of inducing cancer. These terms developed in the context of human medicine where the goal was to predict the likelihood that the tumor found in an individual patient might be lethal. It was noted that tumors with certain characteristics were most likely to be lethal, that is malignant, whereas others did not indicate a bad prognosis. Thus, the terms benign and malignant reflected the expected outcome of the presence of the tumor in the individual patient. They bore no relationship to the causal events leading to these tumors and whether or not such events would produce the same or a different kind of tumor in another individual. The guidelines for distinguishing between benign and malignant tumors are very good with some kinds of tumors, but relatively poor for others. Thus, in the latter case, disagreement may exist among qualified pathologists as to whether a tumor is benign or malignant. The sharp distinction between benign and malignant tumors is also somewhat muddied by the tendency of some kinds of benign tumors to progress onward to malignancy (*32*).

In the experimental bioassay, we are not really interested in whether the tumor will or will not be lethal in the particular mouse or rat. We are interested in whether these tumors indicate that the chemical inducing them is capable of causing cancer under some circumstances in exposed human beings. Thus, the question is whether the tumors represent an index of carcinogenicity of the chemical rather than whether they represent a lethal threat to the animals in which they reside. A number of experimental studies suggest the importance of considering the presence of benign tumors as an indicator that their inducing agent is capable of causing malignancy. The induction of benign adenomas of the mouse lung has been used as an indicator of carcinogenicity. It has been shown that many widely studied chemical carcinogens that are clearly capable of inducing malignancy under some circumstances cause an increase in this tumor type (*49*). Some scientists discounted an early study showing the induction by DDT of mouse liver tumors that were diagnosed as benign (*50*) because no metastases were found. These studies were stopped after 18 months. Subsequent studies lasting for a longer period confirmed this result and also showed the induction of some metastasizing tumors of the liver (*51*). The induction of tumors of the mammary gland

by x-ray and by carcinogenic polycyclic hydrocarbons has been extensively studied in rats. These carcinogenic agents are capable of inducing both malignant adenocarcinomas and benign fibroadenomas of the mammary gland. These tumors are similar to those found in the human breast, and, in humans, as in the rat, the former is clearly malignant and the latter benign. Studies in rats, however, have shown that the relative proportion of these two types of tumors that are induced varies markedly among different genetic strains of rat (*52*), indicating the importance of genetics in determining whether a carcinogen will induce a benign or a malignant tumor. Thus, it has been shown that under some experimental conditions chemicals capable of inducing malignancy will induce mostly benign tumors. It is not clear that there are any chemicals capable only of inducing benign tumors and never inducing malignancies, though the possibility cannot be ruled out that there may be some. As with many other questions, the regulator must make a decision before arguments have ceased within the scientific community. These may either lean toward protecting human health or toward protecting economic enterprise. In the former case a significant increase in benign tumors would be considered to be an index of carcinogenicity unless solid evidence were provided that the particular chemical was only capable of inducing benign tumors. In the latter case less weight might be placed on benign tumors.

In a recent publication, Tomatis (*53*) described the delays that occurred in controlling exposure to a number of human carcinogens. Delays resulted from failure to act on experimental data in the absence of human evidence, failure to act on human evidence in the absence of experimental data, and even failure to act on both human and experimental evidence when tumors induced in animals were of a different type from those found in exposed human populations. Meanwhile, additional humans suffered from continuing induction of cancer. It will always be possible to find arguments for the uncertainty of any set of data on carcinogenicity. Prevention of cancer requires that action be taken on the basis of reasonable evidence of the possibility of hazard even if this may result sometimes in what may be proven later to be unnecessary controls. As further understanding of carcinogenicity develops, it should be possible to reach a greater consensus on risk levels. Action to protect public health cannot be delayed until then.

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